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(71) Applicant *(for all designated States except US)*: **RUTGERS, THE STATE UNIVERSITY** [US/US]; Old Queens Building, Somerset and George Streets, New Brunswick, NJ 08903 (US).

(71) Applicants and
(72) Inventors: **LAVOIE, Edmond, J.** [US/US]; 3 Guilford Court, Princeton Junction, NJ 08550 (US). **SINGH, Sudhir, K.** [IN/IN]; B1, 1701 L & T South City, Arekere Mico Layout, 560076 Bangalore (IN). **LIU, Leroy, F.** [US/US]; 5 Fairacres Drive, Bridgewater, NJ 08807 (US).

(74) Agents: **STEFFEY, Charles, E.** et al.; SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A., P.O. Box 2938, Minneapolis, MN 55402 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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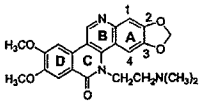
(54) Title: NITRO AND AMINO SUBSTITUTED TOPOISOMERASE AGENTS



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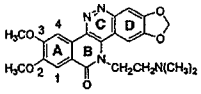

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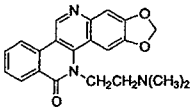

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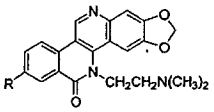

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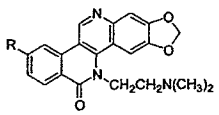

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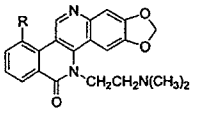

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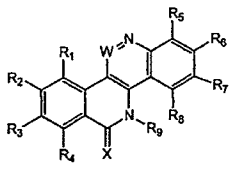

(I)

(57) Abstract: The invention provides compounds of formula (I): wherein R_1-R_9, W, and X have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula (I), processes for preparing compounds of formula (I), intermediates useful for preparing compounds of formula (I), and therapeutic methods for treating cancer using compounds of formula (I).

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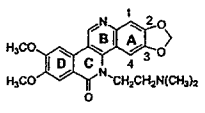

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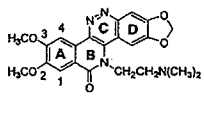

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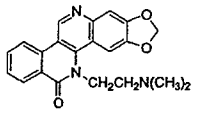

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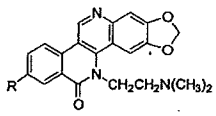

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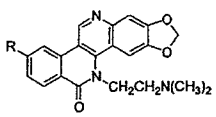

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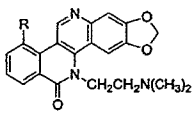

6a R = NO_2
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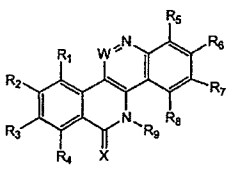

(I)

(57) Abstract: The invention provides compounds of formula (I): wherein R_1-R_9, W, and X have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula (I), processes for preparing compounds of formula (I), intermediates useful for preparing compounds of formula (I), and therapeutic methods for treating cancer using compounds of formula (I).

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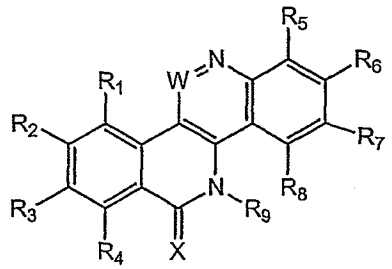


I

wherein:

one of R_1, R_2 and R_3 is nitro or NR_aR_b;

and the remaining R_1, R_2, and R_3 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_1 and R_2, or R_2 and R_3 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_4 is hydrogen, hydroxy, or fluoro;

each R_5, R_6, R_7, and R_8 is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_5 and R_6, R_6 and R_7, or R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more (e.g. 1, 2, 3, or 4) solubilizing groups;

W is N or CH;

X is two hydrogens, =O, =S, or $=NR_e$;

R_a and R_b are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino ring;

each R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

each R_d is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl; and R_e is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition comprising a effective amount of a compound of the invention in combination with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of inhibiting cancer cell growth, comprising administering to a mammal afflicted with cancer, an amount of a compound of the invention, effective to inhibit the growth of said cancer cells.

The invention also provides a method comprising inhibiting cancer cell growth by contacting said cancer cell *in vitro* or *in vivo* with an amount of a compound of the invention, effective to inhibit the growth of said cancer cell.

The invention also provides a compound of the invention for use in medical therapy, preferably for use in treating cancer, for example, solid tumors, as well as the use of a compound of the invention for the manufacture of a medicament useful for the treatment of cancer, for example, solid tumors.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of formula I are useful to prepare other compounds of formula I.

Brief Description of the Figures

Figure 1 shows the structure of compounds of the invention (**4a, 4b, 5a, 5b, 6a, and 6b**) as well as compounds **1, 2,** and **3.**

Figure 2 illustrates the synthesis of representative compounds of formula I (**4a, 4b, 5a, 5b, 6a,** and **6b**) and compound **3.**

Detailed Description

The following definitions are used, unless otherwise described.

"(C_1-C_6)alkyl" denotes both straight and branched carbon chains with 1, 2, 3, 4, 5, or 6, carbon atoms, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer

such as "isopropyl" being specifically referred to.

"(C_3-C_6)cycloalkyl" denotes a carbocyclic ring with 3, 4, 5, or 6, carbon atoms.

"Aryl" denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Examples of aryl include phenyl, indenyl, and naphthyl.

"Aryl(C_1-C_6)alkyl" refers to a group of the formula aryl-(C_1-C_6)alkyl-, where aryl and (C_1-C_6)alkyl are as defined herein.

1. "Solubilizing group (R_z)" is a substituent that increases the water solubility of the compound of formula I compared to the corresponding compound lacking the R_z substituent (i.e. wherein R_z is hydrogen). Examples of solubilizing groups include (C_1-C_6)alkoxycarbonyl (e.g. -CO_2Me), cyano, halo, hydroxy, mercapto, oxo (=O), carboxy (COOH), nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, and -NR_fR_g, wherein R_f and R_g may be the same or different and are chosen from hydrogen, (C_1-C_6)alkyl, and (C_3-C_6)cycloalkyl.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A specific value for W is N.

Another specific value for W is CH.

A specific value for R_1 is nitro.

Another specific value for R_1 is NR_aR_b.

A specific compound of formula (I) is a compound wherein R_2 and R_3 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

A specific compound of formula (I) is a compound wherein R_2 and R_3 are each hydrogen.

A specific value for R_2 is nitro or NR_aR_b.

Another specific value for R_2 is nitro.

Another specific value for R_2 is NR_aR_b.

A specific compound of formula (I) is a compound wherein R_1 and R_3 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

A specific compound of formula (I) is a compound wherein R_1 and R_3 are each hydrogen.

A specific value for R_3 is nitro or NR_aR_b.

Another specific value for R_3 is nitro.

Another specific value for R_3 is NR_aR_b.

A specific compound of formula (I) is a compound wherein R_1 and R_2 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

A specific compound of formula (I) is a compound wherein R_1 and R_2 are each hydrogen.

A specific value for R_4 is hydrogen.

Another specific value for R_4 is fluoro or hydroxy.

A specific compound of formula (I) is a compound wherein one of R_2 and R_3 is nitro or NR_aR_b.

A specific compound of formula (I) is a compound wherein each R_5, R_6, R_7, and R_8 is independently hydrogen, or OR_d.

A specific value for R_5 is hydrogen.

A specific value for R_6 OR_d.

A specific value for R_7 OR_d.

A specific value for R_8 is hydrogen.

A specific compound of formula (I) is a compound wherein or R_5 and R_6 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

A specific compound of formula (I) is a compound wherein or R_6 and R_7 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

A specific compound of formula (I) is a compound wherein R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

A specific value for R_9 is (C_1-C_6)alkyl substituted with one or more hydroxy groups.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one hydroxy group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more mercapto groups.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one mercapto group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more carboxy groups.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one carboxy group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more NR_fR_g groups.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one NR_fR_g group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more NH_2 groups.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one NH_2 group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more $N(CH_3)_2$ groups.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_3)_2$ group.

Another specific value for R_9 is (C_1-C_6)alkyl substituted with one or more $N(CH_2CH_3)_2$ groups.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one $N(CH_2CH_3)_2$ group.

Another specific value for R_9 is a (C_1-C_6)alkyl substituted with one or more (C_1-C_6)alkoxycarbonyl, cyano, halo, hydroxy, mercapto, oxo, carboxy,

nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, or -NR_fR_g groups.

Another specific value for R_9 is a (C_2-C_4)alkyl substituted with one or two groups selected from hydroxy, mercapto, carboxy, amino, methylamino, ethylamino, dimethylamino, and diethylamino.

Another specific value for R_9 is 2-hydroxyethyl.

Another specific value for R_9 is 3-hydroxypropyl.

Another specific value for R_9 is 2-hydroxypropyl.

Another specific value for R_9 is -CH_2CH_2-NR_fR_g wherein R_f and R_f are each independently hydrogen or (C_1-C_6)alkyl.

Another specific value for R_9 is -CH_2CH_2-NR_fR_g wherein R_f and R_f are each independently methyl or ethyl.

A specific compound is any one of compounds **4a**, **4b**, **5a**, **5b**, **6a**, and **6b**; or a pharmaceutically acceptable salt thereof.

Another specific compound is a compound of formula (I) wherein R_1 is hydrogen; R_2 is nitro; R_3 is hydrogen; R_4 is hydrogen; R_5 is hydrogen; R_6 and R_7 taken together are methylenedioxy; R_8 is hydrogen; R_9 is 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

Another specific compound is a compound of formula (I) wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is nitro; R_4 is hydrogen; R_5 is hydrogen; R_6 and R_7 taken together are methylenedioxy; R_8 is hydrogen; R_9 is 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

A compound of formula I can be prepared as described in the Examples below and as illustrated in Figure 2. Reaction of a 4-chloroquinoline with the requisite amine provides compound **7**. Amide formation provides compounds **8b-8d**, which can be cyclized to provide compounds **4a-6a**. Subsequent reduction of the nitro group in compounds **4a-6a** provides aryl amines **4b-6b**.

The starting materials employed in the synthetic methods described herein are commercially available, have been reported in the scientific literature, or can be prepared from readily available starting materials using procedures known in the field. It may be desirable to optionally use a protecting group during all or portions of the above described synthetic procedures. Such protecting groups and methods for their introduction and removal are well known in the art. See Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & Sons, Inc.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine topoisomerase inhibition activity or cytotoxic activity using the standard tests described herein, or using other similar tests which are well known in the art.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic

compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal, for example, sodium, potassium or lithium, or alkaline earth metal, for example calcium, salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, that is, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, for example, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to

otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for

example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example,

see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg per day, e.g., from about 1 to about 60 mg/kg of body weight per day or about 2 to 50 mg/kg per day.

The compound may conveniently be administered in unit dosage form; for example, containing 5 to 1,000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The ability of a compound of the invention to effect topoisomerase I or II mediated DNA cleavage can be determined using pharmacological models that

are well known to the art, for example, using a model like Test A described below.

Test A. **Topoisomerase-mediated DNA cleavage assays**

Human topoisomerase I was expressed in *E. Coli* and isolated as a recombinant fusion protein using a T7 expression system as described by Gatto, B., et al., *Cancer Res.* **1996,** *56*, 2795-2800. Plasmid YepG was purified by the alkali lysis method followed by phenol deproteination and CsCl/ethidium isopycnic centrifugation method as described by Maniatis, T., et al., J. *Molecular Cloning, a Laboratory Manual*; Cold Spring Harbor Laboratory: Cold Spring Harbor, NY 1982; pp 149-185. The end-labeling of the plasmid was accomplished by digestion with a restriction enzyme followed by end-filling with Klenow polymerase as previously described by Tewey, K.M., et al., *Science* **1984**, *226*, 466-468. The cleavage assays were performed as previously reported (see Gatto, B. , et al., *Cancer Res.* **1996,** *56*, 2795-2800; and Wang, H., et al., *Biochemistry* **2001**, *40*; 3316-3323) . The drug and the DNA in presence of topoisomerase I was incubated for 30 minutes at 37 °C. The reactions were terminated by the addition of 5 μl of 5% SDS and 1 mg/ml protein kinase K with an additional 1 hour of incubation at 37 °C. Samples were then alkali denatured by the addition of NaOH, EDTA, sucrose, and bromophenol blue to final concentrations of 75 mM, 2.5%, and 0.05 mg/ml, respectively, prior to loading onto a neutral agarose gel. After development of the gels, typically 24-hour exposure was used to obtain autoradiograms outlining the extent of DNA fragmentation. Topoisomerase I-mediated DNA cleavage values are reported as REC, Relative Effective Concentration, i.e. concentrations relative to topotecan, whose value is arbitrarily assumed as 1.0, that are able to produce the same cleavage on the plasmid DNA in the presence of human topoisomerase I. Data for representative compounds of the invention is provided in Table 1 below.

The cytotoxic effects of a compound of the invention can be determined using pharmacological models that are well known to the art, for example, using a model like Test B described below.

Test B. **Inhibition of Cell Growth: MTT-microtiter plate tetrazolinium cytotoxicity assay (RPMI 8402, CPT-K5 Cells)**

The cytotoxicity was determined using the MTT-microtiter plate tetrazolinium cytotoxicity assay (MTA – See Mosmann, T., *J. Immunol. Methods* **1983**, *65*, 55-63; Carmichael, J., et al., *Cancer Res.* **1987**, *47*, 936-942; and Denizot, F., et al., *J. Immunol. Methods* **1986**, *89*, 271-277). The human lymphoblast RPMI8402 and its camptothecin-resistant variant cell line, CPT-K5 were provided by Dr. Toshiwo Andoh (Aichi Cancer Center Research Institute, Nagoya, Japan – See Andoh, T. , et al., *Adv. in Pharmacology* **1994**, *29B*, 93-103). The cytotoxicity assay was performed using 96-well microtiter plates. Cells were grown in suspension at 37 °C in 5% CO_2 and maintained by regular passage in RPMI medium supplemented with 10% heat- inactivated fetal bovine serum, L-glutamine (2 mM), penicillin (100 U/mL), and streptomycin (0.1 mg/mL). Each well was plated with either 2,000 RPMI8402 cells or 4,000 CPT-K5 cells. For determination of IC_{50}, cells were exposed continuously for 4 days to varying concentrations of drug, and MTT assays were performed at the end of the fourth day. Each assay was performed with a control that did not contain any drug. All assays were performed at least twice in 6 replicate wells. Data for representative compounds is provided in Table 1 below.

Table 1. TOP1-targeting Activity and Cytotoxicity

Compound	TOP1-mediated DNA Cleavage (REC)[a]	Cytotoxicity (IC_{50}; μM)[b]	
		RPMI8402	CPT-K5
1	0.5	0.002	0.9
2	0.3	0.001	0.6
3	6	0.06	0.95
4a	0.2	0.003	0.33
4b	8.0	0.08	0.38
5a	0.1	0.002	2.8
5b	0.5	0.025	1.0
6a	1000	4.8	> 10
6b	15	0.34	3.2
Camptothecin	0.5	0.005	61
CPT-11	25	0.57	>100
Topotecan	1	0.012	> 50
VM-26	>1000	0.22	0.28

[a] TOP1 cleavage values are reported as REC, relative effective concentration, i.e., concentrations relative to topotecan, whose value is arbitrarily assumed as 1, that produce the same degree of cleavage of the plasmid DNA in the presence of human TOP1.

[b] IC_{50} was calculated after 4 days of continuous drug exposure and are the average of two or more replicate assays.

The compounds of the invention can function as cytotoxic agents against tumor cell lines, including multi-drug resistant tumor cell lines. Thus, the compounds are useful to treat cancer and can be used to treat tumors that are resistant to other specific chemotherapeutic agents.

Topoisomerase inhibitors are also known to possess antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, and antiviral activity. Accordingly, the topoisomerase inhibitors of the invention may also be useful as antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoritic, or antiviral agents. In particular, compounds of the invention that demonstrate little or no activity as mammalian topoisomerase I poisons, because of the possibility of similar molecular mechanism of action, could be highly active and selective antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or antiviral agents. Thus, certain compounds of the invention may be particularly useful as

systemic antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or antiviral agents in mammals. The invention also provides the use of a compound of the invention for the manufacture of a medicament useful for producing an antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or antiviral effect in a mammal.

As used herein, the term "solid mammalian tumors" include cancers of the head and neck, lung, mesothelioma, mediastinum, esophagus, stomach, pancreas, hepatobiliary system, small intestine, colon, rectum, anus, kidney, ureter, bladder, prostate, urethra, penis, testis, gynecological organs, ovarian, breast, endocrine system, skin central nervous system; sarcomas of the soft tissue and bone; and melanoma of cutaneous and intraocular origin. The term "hematological malignancies" includes childhood leukemia and lymphomas, Hodgkin's disease, lymphomas of lymphocytic and cutaneous origin, acute and chronic leukemia, plasma cell neoplasm and cancers associated with AIDS. The preferred mammalian species for treatment are humans and domesticated animals.

The invention will now be illustrated by the following non-limiting Examples.

Examples

General Experimental

Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus. Column chromatography refers to flash chromatography conducted on SiliTech 32-63 μm, (ICN Biomedicals, Eschwegge, Ger.) using the solvent systems indicated. Infrared spectral data (IR) were obtained on a Perkin-Elmer 1600 Fourier transform spectrophotometer and are reported in cm^{-1}. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance were recorded on a Varian Gemini-200 Fourier Transform spectrometer. NMR spectra (200 MHz ^{1}H and 50 MHz ^{13}C) were recorded in the deuterated solvent indicated with chemical shifts reported in δ units

downfield from tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Mass spectra were obtained from Washington University Resource for Biomedical and Bio-organic Mass Spectrometry within the Department of Chemistry at Washington University, St. Louis, MO.

Example 1: 8-Nitro-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*][1,6]naphthyridin-6-one (4a).

A mixture of compound **8b** (125 mg, 0.25 mmol), $Pd(OAc)_2$ (11.25 mg , 0.05 mmol), Ag_2CO_3 (137.5 mg, 0.5 mmol), P(*o*-tolyl)$_3$ (30.5 mg, 0.1 mmol) and anhyd. DMF (10 mL) was heated at 150 °C for 30 min. The reaction mixture was cooled to room temperature, filtered through Celite and washed with $CHCl_3$ (20 mL) and CH_3OH (10 mL). The solvent was removed in vacuo to provide a dark solid, which was purified by flash chromatography by eluting with $CHCl_3$ and 2% methanol to give 15 mg of a yellow solid (14.4% yield); mp 219-20 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 6H), 2.97 (t, 2H, J= 7), 4.71 (t, 2H, J=6.8), 6.20 (s, 2H), 7.49 (s, 1H), 7.88 (s, 1H) 8.48 (d, 1H, J=8.8), 8.61 (dd, 1H, J=2.6, 9.2) , 9.35 (d, 1H, J=2.2), 9.47 (s, 1H); ^{13}C NMR($CDCl_3$) δ 45.6, 49.6, 57.4, 101.3, 102.5, 107.3, 110.5, 114.6, 122.7, 124.9, 125.7, 127.2, 137.7, 143.4, 143.9, 147.2, 148.2, 148.8, 151.2, 163.3; HRMS *m/z* calcd for $C_{21}H_{18}N_5O_5H$: 407.1356; found 407.1369.

The intermediate compound **8b** was prepared as follows.

a. N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylethane-1,2-diamine (7). The requisite chloroquiniline was stirred in refluxing phenol (5.5 mol equiv.) for 2.5 h. The temperature was lowered to 100 °C and N,N-dimethylethylenediamine (2.55 g, 29 mmol) was added with stirring. The reaction was allowed to stir at 100 °C for 24 hours and the phenol was removed by Kugelrohr distillation under reduced pressure. The residue was partitioned

between $CHCl_3$ and 10% NaOH. The aqueous layer was repeatedly extracted with $CHCl_3$. All of the $CHCl_3$ solutions (initial partition and extracts) were combined and dried ($MgSO_4$) to provide compound **7** in 54% yield; mp 193-194 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 2.70 (t, 2H, J = 6.6), 3.29 (m, 2H), 5.62 (br, 1H), 6.10 (s, 2H), 6.36 (d, 1H, J = 5.3), 7.10 (s, 1H), 7.34 (s, 1H), 8.40 (d, 1H, J = 5.3); ^{13}C NMR ($CDCl_3$) δ 40.1, 45.2, 57.2, 96.3, 98.9, 101.6, 106.5, 114.4, 145.2, 146.8, 148.9, 149.7, 150.1; HRMS calcd for $C_{14}H_{17}N_3O_2$: 260.1399; found 260.1377.

b. N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-bromo-5-nitrobenzamide (8b). To a solution of compound **7** (259 mg, 1.0 mmol) and triethylamine (0.5 mL) in dry CH_2Cl_2 (20 mL) was added a solution of 2-bromo-5-nitrobenzoic acid chloride in 20 mL of CH_2Cl_2 (which was prepared by refluxing of 295 mg, 1.2 mmol of 2-bromo-5-nitrobenzoic acid in 10 mL of thionyl chloride for 3 h.) and reaction mixture was heated to reflux for 4 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. The solvent was removed in vacuo to give a yellow solid; yield 350 mg (71.8%); mp 204-5 °C; ^{1}H NMR ($CDCl_3$) δ (2.3, s, 6H), 2.53-2.64 (m, 2H), 3.67-3.81 (m, 1H), 4.42-4.55 (m, 1H), 6.19 (s, 2H), 7.31 (s, 1H), 7.34 (d, 1H, J = 4.8), 7.43 (s, 1H), 7.52 (d, 1H, J = 8.8), 7.76 (dd, 1H, J = 2.6, 8.4), 7.87 (d, 1H, J = 2.6), 8.53 (d, 1H, J = 4.8); ^{13}C NMR ($CDCl_3$) δ 45.4, 46.6, 56.4, 97.9, 102.4, 106.6, 119.4, 122.3, 122.8, 124.6, 127.2, 134.0, 139.0, 144.5, 145.9, 148.1, 148.5, 149.6, 151.5, 166.5.

Example 2: 8-Amino-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (4b)

To a solution of compound **4a** (40 mg, 0.1 mmol) in ethanol (10 mL), Ra-Ni (~50 mg) then hydrazine hydrate (0.2 mL) were added and the reaction stirred at room temperature for 3h. The catalyst was filtered through the Celite and filtrate was concentrated in vacuo to provide 26 mg of a solid (69.1% yield); mp 245-246 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H), 3.01 (t, 2H, J = 7.4), 4.11(s, 2H), 4.68 (t, 2H, J = 7.4), 6.17(s, 2H,), 7.18 (dd, 1H, J = 2.8, 11.4), 7.46 (s, 1H) 7.71 (d, 1H, J = 3), 7.80 (s,1H) 8.20 (d, 1H, J = 8.8), 9.40 (s, 1H); HRMS *m/z* calcd for $C_{21}H_{20}N_4O_3H$: 377.1614; found 377.1604.

Example 3: 9-Nitro-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (5a).

A mixture of compound **8c** (125 mg, 0.25 mmol), $Pd(OAc)_2$ (11.25 mg , 0.05 mmol), Ag_2CO_3 (137.5 mg, 0.5 mmol), P(*o*-tolyl)$_3$ (30.5 mg, 0.1 mmol) and anhyd. DMF (10 mL) was heated at 150 °C for 2h. The reaction mixture was cooled to room temperature, filtered through Celite, and washed with $CHCl_3$ (20 mL) and CH_3OH (10 mL). The solvent was removed in vacuo to provide a dark solid, which was purified by flash chromatography by eluting with $CHCl_3$ and 1% methanol to provide 40 mg of a yellow solid in 38.4% yield; mp 258-259 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 2.96 (t, 2H, J = 6.4), 4.71 (t, 2H, J = 6.6), 6.22 (s, 2H) 7.52 (s, 1H), 7.88 (s, 1H), 8.37 (dd, 1H, J = 1.8, 8.6), 8.66 (d, 1H, J = 8.8), 9.22 (d, 1H, J = 1.8), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.6, 49.6, 57.2, 101.1, 102.5, 107.3, 110.8, 114.6, 117.0,121.9, 128.8, 130.9, 133.9, 142.6, 143.4, 148.2, 148.6, 150.9, 151.0, 163.3; HRMS *m/z* calcd for $C_{21}H_{18}N_4O_5H$: 407.1356; found 407.1339.

The intermediate compound **8c** was prepared as follows.

a. N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-bromo-4-nitrobenzamide (8c). To a solution of compound 7 (259 mg, 1.0 mmol) and triethylamine (0.5 mL) in dry CH_2Cl_2 (20 mL) was added a solution of 2-bromo-4-nitrobenzoic acid chloride in 20 mL of CH_2Cl_2 (which was prepared by refluxing of 295 mg, 1.2 mmol of 2-bromo-4-nitrobenzoic acid in 10 mL of thionyl chloride for 4 h). The reaction mixture was heated to reflux for 6 h. The reaction mixture was allowed to cool and was then washed with saturated $NaHCO_3$ solution, water and brine and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo to give a yellow solid; yield 345 mg (70.8%); mp 111-112 °C; ^{1}H NMR ($CDCl_3$) δ (2.29, s, 6H), 2.60 (t, 2H, J = 6.2), 3.62-3.72 (m, 1H), 4.49-4.62 (m, 1H), 6.19 (d, 2H, J = 5.6), 7.12 (d, 1H, J = 8.2), 7.37 (s, 3H), 7.75 (d, 1H, J = 8) 8.26 (s, 1H), 8.5 (d, 1H, J = 4.6); ^{13}C NMR($CDCl_3$) δ 45.4, 46.6, 56.4, 97.8, 102.4, 106.7, 119.5, 120.6, 121.7, 122.7, 127.6, 128.1, 143.6, 144.4, 147.9, 148.2, 148.5, 149.5, 151.4, 166.8.

Example 4: 9-Amino-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (5b).

To a solution of compound **5a** (40 mg, 0.1 mmol) in ethanol (10 mL), Ra-Ni (~50 mg) and then hydrazine hydrate (0.2 mL) were added and the reaction stirred at room temperature for 3 h. The catalyst was filtered through Celite and filtrate was concentrated in vacuo to provide 23 mg of a solid (61.1% yield); mp 300-301 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H), 3.01 (t, 2H, J = 6.6), 4.33 (s, 2H), 4.63 (t, 2H, J =7), 6.18 (s, 2H), 6.91(dd, 1H, J = 2.2, 8.8), 7.46 (s, 1H), 7.45 (d, 1H, J = 2.2), 7.83 (s, 1H), 8.30 (d, 1H, J = 8.8), 9.35 (s, 1H); HRMS *m/z* calcd for $C_{21}H_{20}N_4O_3H$: 377.1614; found 377.1606.

Example 5: 10-Nitro-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (6a).

A mixture of compound **8d** (125 mg, 0.25 mmol), $Pd(OAc)_2$ (11.25 mg , 0.05 mmol), Ag_2CO_3 (137.5 mg, 0.5 mmol), P(*o*-tolyl)$_3$ (30.5 mg, 0.1 mmol) and anhyd. DMF (10 mL) was heated at 150 °C for 2h. The reaction mixture was cooled to room temperature, filtered through Celite and washed with $CHCl_3$ (20 mL) and CH_3OH (10 mL). The solvent was removed in vacuo to yield a dark solid, which was purified by flash chromatography by eluting with $CHCl_3$ and 1% methanol to provide 35 mg of a yellow solid in 33.6% yield; mp 189-90 °C; ^{1}H NMR ($CDCl_3$) δ (2.28, s, 6H), 2.90 (t, 2H, *J* = 7), 4.69 (t, 2H, *J* = 7), 6.20 (s, 2H), 7.44 (s, 1H), 7.67 (t, 1H, *J* = 8.8) 7.79 (s, 1H), 8.03 (dd, 1H, *J* = 1.4, 8) 8.71 (dd, 1H, *J* = 1.4, 7.6), 8.85 (s, 1H); HRMS *m/z* calcd for $C_{21}H_{18}N4O_5H$: 407.1356; found 407.1351.

The intermediate compound **8d** was prepared as follows.

a. N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-bromo-3-nitrobenzamide (8d). To a solution of compound 7 (259 mg, 1.0 mmol) and triethylamine (0.5 mL) in dry CH_2Cl_2 (20 mL) was added a solution of 2-bromo-3-nitrobenzoic acid chloride in 20 mL of CH_2Cl_2 (which was prepared by refluxing of 295 mg, 1.2 mmol of 2-bromo-3-nitrobenzoic acid in 10 mL of thionyl chloride for 4 h). The reaction mixture was heated to reflux for 6 h. The reaction mixture was allowed to cool and then washed with saturated $NaHCO_3$ solution, water and brine and dried over Na_2SO_4. Solvent was removed in vacuo to give 360 mg of a yellow solid (73.9%); mp 96-97 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.62 (t, 2H, *J* = 6.6), 3.59-3.69 (m, 1H), 4.53-4.67 (m, 1H), 6.18 (d, 2H, *J* = 5.2), 7.05 (d, 1H, *J* = 7.8), 7.14 (d, 1H, *J* = 7.4) 7.28-7.36 (m, 3H) 7.50 (dd, 1H, *J* = 1.2, 7.8) , 8.55 (d, 1H, *J* = 3.8); ^{13}C NMR ($CDCl_3$) δ 45.4, 46.5, 56.4, 97.8, 102.3, 106.7, 112.2, 119.5, 122.6, 125.2, 127.7, 129.7, 140.8, 144.6, 148.3, 148.5, 149.5, 151.4, 166.9

Example 6: 10-Amino-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*][1,6]naphthyridin-6-one (6b).

To a solution of compound **6a** (40 mg, 0.1 mmol) in ethanol (10 mL), Ra-Ni (~50 mg) and then hydrazine hydrate (0.2 mL) were added and reaction was stirred at room temperature for 3 h. The catalyst was filtered through the Celite and filtrate was concentrated in vacuo to provide 28 mg of a solid (74.4% yield); mp 223-224 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 6H), 2.90 (t, 2H, J = 7), 4.34 (s, 2H), 4.65 (t, 2H, J =7.4), 6.18 (s, 2H,), 7.16 (d, 1H, J = 8), 7.4 (dd, 2H, J = 7.6, 9.8) 7.74 (s, 1H), 8.02 (d, 1H, J = 7.8) , 10.03 (s, 1H) ; HRMS *m/z* calcd for $C_{21}H_{20}N_4O_3H$: 377.1614; found 377.1631.

Example 7 The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
'Compound X'	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
'Compound X'	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
'Compound X'	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
'Compound X' (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
'Compound X' (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution	

(pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
'Compound X'	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

Comparative Example 1: 2,3-Methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c*,*h*]1,6-naphthyridin-6-one (3).

A mixture of **8a** (343 mg, 0.7 mmol), $Pd(OAc)_2$ (31.5 mg, 0.14 mmol), P(*o*-tolyl)$_3$ (85.4 mg, 0.28 mmol), and silver carbonate (385 mg, 1.4 mmol) were heated to reflux in DMF (21 mL) and stirred under nitrogen for 15 minutes, then the mixture was cooled and diluted with chloroform, filtered through Celite, and evaporated, and the crude product was chromatographed in 197:3 chloroform-methanol, to provide 95 mg, in 38% yield; mp 200.5-202 °C; IR ($CHCl_3$) 1656; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 6H), 3.06 (t, 2H, J = 6.5), 4.67 (t, 2H, J = 6.5), 6.28 (s, 2H), 7.44 (m, 1H), 7.68 (t, 1H, J = 7.6), 7.79 (s, 1H), 7.92 (td, 1H, J = 7.6, J = 1.4), 8.34 (dd, 1H, J = 8.1, J=1.4), 8.68 (d, 1H, J = 8.1), 9.63 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 45.1, 47.8, 56.9, 101.6, 103.3, 107.0, 112.3, 114.7, 122.8, 125.3, 128.7, 129.3, 133.1, 134.4, 141.4, 144.7, 148.0, 148.1, 150.8, 164.4.

The intermediate compound **8a** was prepared as follows.

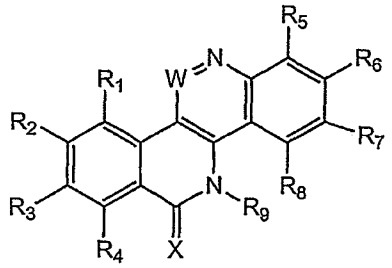
a. **N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodobenzamide (8a).** Oxalyl chloride (1.05 g, 8.1 mmol) was added to a solution of *o*-iodobenzoic acid (0.57 g, 2.3 mmol) in methylene chloride (20 mL)

under nitrogen, and the stirred mixture refluxed for 4 h. The mixture was then concentrated to dryness under vacuum. The acid chloride was redissolved in methylene chloride (20 mL) and added to a solution of compound 7 and triethylamine (2.0 g, 20.0 mmol) in methylene chloride (20 mL). The reaction was stirred at reflux under nitrogen for 2 h. The mixture was then cooled and washed with a saturated solution of sodium bicarbonate (3 x 75 mL), and extracted into dilute HCl (3 x 75 mL), and the combined aqueous extracts were washed with chloroform (75 mL), made basic using 30 % NaOH, then extracted with chloroform (3 x 75 mL). The combined organic extracts were washed with brine (100 mL), dried (anhydrous $MgSO_4$), and concentrated *in vacuo*, to give 795 mg, in 84% yield; IR ($CHCl_3$) 1653; ^1H NMR ($CDCl_3$) δ 2.23 (s, 6H), 2.60 (m, 2H), 3.52 (m, 1H), 4.57 (m, 1H), 6.13 (d, 1H, $J = 0.7$), 6.16 (d, 1H, $J = 0.7$), 6.78 (m, 3H), 7.32 (m, 2H), 7.36 (s, 1H), 7.64 (d, 1H, $J = 7.6$), 8.48 (d, 1H, $J = 4.8$); ^{13}C NMR ($CDCl_3$) δ 45.6, 46.8, 56.5, 93.9, 98.4, 102.3, 106.5, 120.2, 122.8, 126.5, 127.2, 128.3, 130.2, 139.5, 141.5, 145.6, 148.2, 149.2, 151.2, 170.0.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of formula I:



I

wherein:

one of R_1, R_2 and R_3 is nitro or NR_aR_b;

and the remaining R_1, R_2, and R_3 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_1 and R_2, or R_2 and R_3 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_4 is hydrogen, hydroxy, or fluoro;

each R_5, R_6, R_7, and R_8 is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, NR_aR_b, $COOR_c$, OR_d; or R_5 and R_6, R_6 and R_7, or R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy;

R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more solubilizing groups;

W is N or CH;

X is two hydrogens, =O, =S, or $=NR_e$;

R_a and R_b are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino ring;

each R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

each R_d is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl; and R_e is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, or aryl$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein W is N.

3. The compound of claim 1 wherein W is CH.

4. The compound of any one of claims 1-3 wherein R_1 is nitro.

5. The compound of any one of claims 1-3 wherein R_1 is NR_aR_b.

6. The compound of any one of claims 1-5 wherein R_2 and R_3 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or $(C_1$-$C_6)$alkyl.

7. The compound of any one of claims 1-5 wherein R_2 and R_3 are each hydrogen.

8. The compound of any one of claims 1-3 wherein R_2 is nitro or NR_aR_b.

9. The compound of any one of claims 1-3 wherein R_2 is nitro.

10. The compound of any one of claims 1-3 wherein R_2 is NR_aR_b.

11. The compound of any one of claims 1-3 and 8-10 wherein R_1 and R_3 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or $(C_1$-$C_6)$alkyl.

12. The compound of any one of claims 1-3 and 8-10 wherein R_1 and R_3 are each hydrogen.

13. The compound of any one of claims 1-3 wherein R_3 is nitro or NR_aR_b.

14. The compound of any one of claims 1-3 wherein R_3 is nitro.

15. The compound of any one of claims 1-3 wherein R_3 is NR_aR_b.

16. The compound of any one of claims 1-3, 13-15 wherein R_1 and R_2 are each independently hydrogen, or OR_d, wherein each R_d is hydrogen or (C_1-C_6)alkyl.

17. The compound of any one of claims 1-3, 13-15 wherein R_1 and R_2 are each hydrogen.

18. The compound of any one of claims 1-17 wherein R_4 is hydrogen.

19. The compound of any one of claims 1-17 wherein R_4 is fluoro or hydroxy.

20. The compound of claim 1, 18, or 19 wherein one of R_2 and R_3 is nitro or NR_aR_b.

21. The compound of any one of claims 1-20 wherein each R_5, R_6, R_7, and R_8 is independently hydrogen, or OR_d.

22. The compound of any one of claims 1-20 wherein R_5 is hydrogen.

23. The compound of any one of claims 1-22 wherein each R_6 OR_d.

24. The compound of any one of claims 1-22 wherein each R_7 OR_d.

25. The compound of any one of claims 1-24 wherein each R_8 is hydrogen.

26. The compound of any one of claims 1-19 and 24 and 25 wherein R_5 and R_6 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

27. The compound of any one of claims 1-19, 22 and 25 wherein R_6 and R_7 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

28. The compound of any one of claims 1-23 wherein R_7 and R_8 taken together are methylenedioxy, 1,2-ethylenedioxy, or 1,3-propylenedioxy.

29. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one or more hydroxy groups.

30. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one hydroxy group.

31. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one or more mercapto groups.

32. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one mercapto group.

33. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one or more carboxy groups.

34. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one carboxy group.

35. The compound of any one of claims 1-28 wherein R_9 is (C_1-C_6)alkyl substituted with one or more NR_fR_g groups.

36. The compound of any one of claims 1-28 wherein R_9 is $(C_1\text{-}C_6)$alkyl substituted with one NR_fR_g group.

37. The compound of any one of claims 1-28 wherein R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more NH_2 groups.

38. The compound of any one of claims 1-28 wherein R_9 is a $(C_1\text{-}C_6)$alkyl substituted with one NH_2 group.

39. The compound of any one of claims 1-28 wherein R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more $N(CH_3)_2$ groups.

40. The compound of any one of claims 1-28 wherein R_9 is a $(C_1\text{-}C_6)$alkyl substituted with one $N(CH_3)_2$ group.

41. The compound of any one of claims 1-28 wherein R_9 is $(C_1\text{-}C_6)$alkyl substituted with one or more $N(CH_2CH_3)_2$ groups.

42. The compound of any one of claims 1-28 wherein R_9 is a $(C_1\text{-}C_6)$alkyl substituted with one $N(CH_2CH_3)_2$ group.

43. The compound of any one of claims 1-28 wherein R_9 is a $(C_1\text{-}C_6)$alkyl substituted with one or more $(C_1\text{-}C_6)$alkoxycarbonyl , cyano, halo, hydroxy, mercapto, oxo, carboxy, nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolinyl, piperazinyl, morpholinyl, thiomorpholinyl, or $-NR_fR_g$ groups, wherein R_f and R_g may be the same or different and are chosen from hydrogen, $(C_1\text{-}C_6)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl.

44. The compound of any one of claims 1-28 wherein R_9 is a (C_2-C_4)alkyl substituted with one or two groups selected from hydroxy, mercapto, carboxy, amino, methylamino, ethylamino, dimethylamino, and diethylamino.

45. The compound of any one of claims 1-28 wherein R_9 is 2-hydroxyethyl.

46. The compound of any one of claims 1-28 wherein R_9 is 3-hydroxypropyl.

47. The compound of any one of claims 1-28 wherein R_9 is 2-hydroxypropyl.

48. The compound of any one of claims 1-28 wherein R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently hydrogen or (C_1-C_6)alkyl.

49. The compound of any one of claims 1-28 wherein R_9 is $-CH_2CH_2-NR_fR_g$ wherein R_f and R_f are each independently methyl or ethyl.

50. Any one of compounds **4a**, **4b**, **5a**, **5b**, **6a**, and **6b**; or a pharmaceutically acceptable salt thereof.

51. The compound of claim 1 wherein R_1 is hydrogen; R_2 is nitro; R_3 is hydrogen; R_4 is hydrogen; R_5 is hydrogen; R_6 and R_7 taken together are methylenedioxy; R_8 is hydrogen; R_9 is 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1 wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is nitro; R_4 is hydrogen; R_5 is hydrogen; R_6 and R_7 taken together are methylenedioxy; R_8 is hydrogen; R_9 is 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*-diethylamino)ethyl; W is N or CH; and X is =O; or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising a compound as described in any one of claims 1-52 in combination with a pharmaceutically acceptable diluent or carrier.

54. A method of inhibiting cancer cell growth, comprising administering to a mammal afflicted with cancer, an amount of a compound as described in any one of claims 1-52, effective to inhibit the growth of said cancer cells.

55. A method comprising inhibiting cancer cell growth by contacting said cancer cell in vitro or in vivo with an amount of a compound as described in any one of claims 1-52, effective to inhibit the growth of said cancer cell.

56. A compound as described in any one of claims 1-52 for use in medical therapy.

57. The compound of claim 56 wherein the therapy is treating cancer.

58. The use of a compound as described in any one of claims 1-52 for the manufacture of a medicament useful for the treatment of cancer.

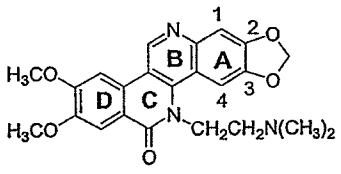
59. A method of producing an antibacterial effect in a mammal in need of such treatment comprising administering to the mammal, an amount of a compound as described in any one of claims 1-52, effective to provide an antibacterial effect.

60. A method of producing an antifungal effect in a mammal in need of such treatment comprising administering to the mammal, an amount of a compound as described in any one of claims 1-52, effective to provide an antifungal effect.

61. The use of a compound as described in any one of claims 1-52 for the manufacture of a medicament useful for producing an antibacterial, antifungal, antiprotozoal, antihelmetic, antipsoriatic, or antiviral effect in a mammal.

62. The use of a compound as described in any one of claims 1-52 for the manufacture of a medicament useful for producing an antifungal effect in a mammal.

Figure 1



1

2

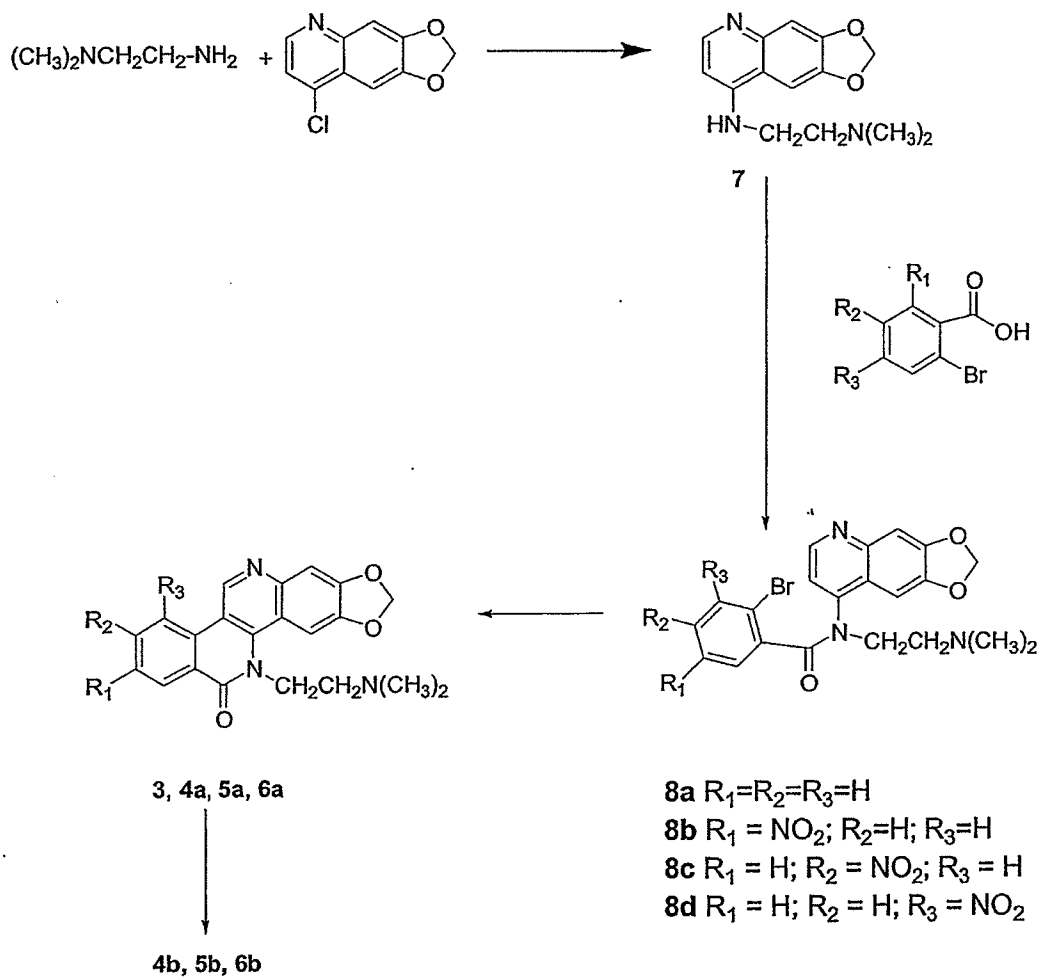
3

4a R = NO_2
4b R = NH_2

5a R = NO_2
5b R = NH_2

6a R = NO_2
6b R = NH_2

Figure 2


(CH3)2NCH2CH2-NH2
Cl
HN-CH2CH2N(CH3)2
7
R1
R2
R3
OH
Br
N-CH2CH2N(CH3)2
3, 4a, 5a, 6a
4b, 5b, 6b
8a R1=R2=R3=H
8b R1 = NO2; R2=H; R3=H
8c R1 = H; R2 = NO2; R3 = H
8d R1 = H; R2 = H; R3 = NO2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/25110

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/14 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	S.K. SINGH ET AL: "Nitro and amino Substitution in the D-Ring of 5-(2-Dimethylaminoethyl)-2,3-methylenedioxy-5H-dibenzo'c,h!'1,6!naphthyridin-6-ones: Effect on Topoisomerase-I Targeting Activity and Cytotoxicity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 11, 2003, pages 2254-2257, XP002264963 schemes 1,2; table 1 ---	1-62
A	WO 01 32631 A (LAVOIE EDMOND J ;LIU LEROY FONG (US); UNIV RUTGERS (US); YU YOUNON) 10 May 2001 (2001-05-10) cited in the application page 3, line 2 -page 3, line 4; claims 1-14; examples 1-10 --- -/--	1-62

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2004	20/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/US 03/25110

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 140 328 A (LAVOIE EDMOND J ET AL) 31 October 2000 (2000-10-31) cited in the application column 2, line 16 -column 2, line 20; claims 1-31; examples 1-6	1-62